

**Remarks**

Claims 1-50 are pending in the present application. Claims 12-20 have been withdrawn. Claims 1, 9, 18, 19, 24 and 25 are amended herein. Claims 4, 12-17, and 37-50 are cancelled herein without prejudice or disclaimer. Claims 51-58 are added herein to complete the record. Support for these amendments and new claims can be found throughout the specification and claims as originally filed. For example, claims reciting density limitations without the use of "about" (amended claim 10, amended claim 25, new claims 51 and 55) are inherently described in original claims 10 and 11 (M.P.E.P. § 2163.05(III)). New claims 52-54 and 56-58 are supported, inter alia, by the specification at page 27, line 4 to page 28, line 16, and at page 34, lines 23-25.

No new matter is added by these amendments and new claims, and their entry and substantive examination are respectfully requested.

**I. Applicant Interview Summary**

Applicants concur with the Examiner's Interview Summary, mailed September 14, 2007, regarding the matters discussed during the September 5, 2007 telephone interview, that possible claim amendments to the independent claims to include length and density limitations were discussed, and that such amendments should overcome the claim rejections under section 102. Applicants also concur that the Guo et al. (1994) article of the 103 rejection was discussed with regard to the oligonucleotide probe density.

**II. Information Disclosure Statement**

An Information Disclosure Statement is submitted with the present response. It is respectfully requested that this Information Disclosure Statement be considered and made of record in the present application.

**III. Claim Rejections—35 U.S.C. § 112, 2nd paragraph, Indefiniteness**

Claims 41 and 45 are rejected under 35 U.S.C. § 112, 2nd paragraph, as indefinite. These claims have been cancelled herein by Applicants, rendering this rejection moot. Accordingly, Applicants respectfully request that this rejection be withdrawn.

#### **IV. Claim Rejections—35 U.S.C. § 102**

##### **A. Brennan et al.**

Claims 1-3, 6-8 and 21-24 are rejected under 35 U.S.C. § 102(b) by U.S. Patent No. 5,474,796 to Brennan. While Applicants still disagree that the Brennan reference is sufficient to anticipate these claims, in order to expedite the prosecution of this application, claim 1 has been amended herein to include the surface density limitations of claim 10, which is free of this rejection. Accordingly, Applicants respectfully request that this rejection be withdrawn.

##### **B. Apple et al.**

Claims 25, 26, 33, 38, 39 and 46 are rejected under 35 U.S.C. § 102(b) by U.S. Patent No. 5,451,512 to Apple et al. Apple et al. discusses the use of a reverse dot-blot procedure to detect HLA-A polymorphisms.

Independent claim 25 is amended herein to incorporate the density limitation of from 250 to 450 angstrom<sup>2</sup>/molecule. This density limitation distinguishes Apple et al., which concerns the use of a reverse dot-blot procedure, and which does not contain this density limitation.

Claims 38, 39 and 46 are cancelled herein. Claims 26 and 33 depend from and incorporate the limitations found in independent claim 25, which contains the density limitation mentioned above. Apple et al. does not teach of an array having this density, and accordingly, Applicants respectfully request that this rejection of claims 25, 26, 33, 38, 39 and 46 be withdrawn.

##### **C. Andrien et al.**

Claims 25, 27, 28, 38 and 40 are rejected under 35 U.S.C. § 102(b) by PCT Patent Publication WO 9421818 to Andrien et al. Andrien et al., similar to Apple et al. above, discusses the use of a reverse dot-blot for the detection of HLB-B alleles. As noted above, independent claim 25 is amended herein to incorporate the density limitation: from 250 to 450 angstrom<sup>2</sup>/molecule. This density limitation distinguishes Andrien et al., which concerns the use of a reverse dot-blot procedure, and which does not contain this limitation.

Claims 38 and 40 are cancelled herein. Claims 27 and 28 depend from and incorporate the limitations found in independent claim 25. Accordingly, Applicants respectfully request that this rejection of claim 25, 27, 28, 38 and 40 under § 102(b) be withdrawn.

**V. Claim Rejections—35 U.S.C. § 103**

**A. Bettinotti et al. in view of Sapolsky et al.**

Claims 1-8, 21-33 and 38-46 are rejected under 35 U.S.C. § 103(a) over Bettinotti et al. (1997) in view of European Patent No. EP0785280 to Sapolsky et al. (1997). As noted on Page 10 of the Office Action, the Examiner maintains that Sapolsky et al. teaches that "polymorphic DNA content may be resolved by using any array of oligonucleotide probes." This rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, three requirements must be satisfied (M.P.E.P. § 2143). First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the proposed modification or combination of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Finally, the prior art reference or combination of references must teach or suggest all of the limitations of the claims. *See In re Wilson* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art").

Further, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both come from the prior art, not from Applicants' disclosure. *See In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); M.P.E.P. § 2143.

Applicants maintain that the skilled artisan would not be motivated to combine the teachings of Bettinotti et al. with Sapolsky et al. to form the array taught by Applicants. Bettinotti et al. only discusses direct sequencing of HLA loci, not of probe design, and Sapolsky et al. only discusses detection of single-base polymorphisms in a stretch of nucleotides, which is not applicable to the highly polymorphic HLA loci, as discussed below.

Instead of describing probes to identify specific alleles, Bettinotti et al. uses nested pcr with primers spanning regions of the HLA loci, and directly sequences the pcr products. Even

with this approach, Bettinotti notes of page 427, right column, middle of second paragraph: "The real challenge was to find a combination of primers that could effectively amplify all alleles at a given locus."

The skilled artisan would not have a reasonable expectation of success of using the arrays detailed in Sapolsky et al. to analyze HLA locus polymorphisms. Sapolsky et al. states in the paragraph on page 2, lines 27-36: "In the human genome, *single-base polymorphisms occur roughly once per 300 bp*," and "*useful polymorphisms...can be found approximately once per kilobase*." (emphasis added). The design of the arrays in Sapolsky et al. follows this underlying theory, and the probes are designed to detect a single nucleotide polymorphism among a stretch of sequence (see, for example, Figure 3).

In contrast to the polymorphisms screened for in the methods of Sapolsky et al., and as noted in Applicants' specification on page 2, lines 14-15, "The human major histocompatibility genes are among the most polymorphic genes known in the human genome." Applicants' arrays for typing HLA loci have to account for this high level of polymorphisms in their probe designs, as described in the specification: "The key feature of the oligonucleotide array assay is the high redundancy of oligonucleotide probes." (page 33, lines 14-15).

Nevertheless, as noted above, in order to expedite the prosecution of this application, Applicants have amended independent claims 1 and 25 to incorporate the density limitation of claim 10, which is free of this rejection. Neither Bettinotti et al. nor Sapolsky et al. teach of an array having this density range, therefore the references alone or in combination do not teach or suggest all of the claim limitations.

In light of the above discussion and claim amendments, the combination of Bettinotti et al. and Sapolsky et al. is insufficient to present a *prima facie* showing of obviousness. Claims 38-46 have been cancelled herein. Claims 2-8 and 21-24 depend from and incorporate the limitations of claim 1, including the density limitation mentioned above. Claims 26-33 depend from and incorporate the limitations of independent claim 25, also including the density limitation. Therefore it is respectfully requested that this rejection of claims 1-8, 21-33 and 38-46 under § 103(a) be withdrawn.

**B. Bettinotti et al. in view of Sapolsky et al. and further in view of McGall et al.**

Claims 9, 34 and 47 are rejected over Bettinotti et al. (1997) in view of European Patent No. EP0785280 to Sapolsky et al. (1997), and further in view of U.S. Patent No. 5,412,087 to McGall et al. Applicants' claims 9, 34 and 37 recite a microarray wherein the solid support comprises glass.

As noted above, the combination of Bettinotti et al. and Sapolsky et al. does not teach how to create arrays to detect polymorphisms of the HLA loci, and the addition of the McGall et al. reference does not remedy this deficiency. Also as noted above, Applicants have amended independent claim 1, from which claim 9 depends, and claim 25, from which claim 34 depends, to incorporate the density limitation of claim 10, which is free of this rejection. Claim 47 has been cancelled. Neither Bettinotti et al. nor Sapolsky et al. teach of an array having this density range, and the McGall et al. reference also does not teach this limitation.

Therefore it is respectfully asserted that the combination of Bettinotti et al., Sapolsky et al. and McGall et al. is insufficient to present a *prima facie* showing of obviousness. Accordingly, it is respectfully requested that this rejection of claims 9, 34 and 47 under § 103(a) be withdrawn.

**C. Bettinotti et al. in view of Sapolsky et al. and further in view of Lockhart et al.**

Claims 10 and 11 are rejected under 35 U.S.C. § 103(a) over Bettinotti et al. (1997) in view of European Patent No. EP0785280 to Sapolsky et al. (1997), and further in view of U.S. Patent No. 5,556,752 to Lockhart et al.

Claim 10 recites that the oligonucleotide probes are present on the solid support at a surface density of from about 250 to about 450 angstrom<sup>2</sup>/molecule. Claim 11 recites that the oligonucleotide probes are present on the solid support at a surface density of from about 325 to about 375 angstrom<sup>2</sup>/molecule.

The Office Action states that the description in Lockhart et al. of oligonucleotides found on an array that are approximately 100 angstroms apart is necessarily the same as the surface density ranges recited in claims 10 and 11. Applicants respectfully disagree.

First, for the reasons stated above, even without the density limitations, claims 1-8 are not obvious over Bettinotti et al. in view of Sapolsky et al., and the elements and suggestions missing

from these references are not provided by Lockhart et al.

Further, Applicants maintain that the type of array found in Lockhart et al. is qualitatively different from the array examples disclosed by Applicants' specification. The array of Lockhart et al. consists of "unimolecular, double-stranded oligonucleotides" (column 2, lines 31-40 and lines 51-59; Figures 1a-1f). The exemplary array comprises 16 separate, unimolecular DNA molecules formed onto the surface of the array (column 21, lines 33-50). Each single molecule had an average spacing of approximately 100 angstroms (column 22, lines 54-59).

The probes of the present invention are not intended to participate in the formation of a duplex as found in Lockhart et al. The probes of Lockhart et al. are intended to form a duplex. See Lockhart at column 2, lines 31-40 and lines 51-59; Figures 1a-1f. The probes of Lockhart are spaced such that it is possible that the outer strand of one molecule form a double-stranded structure with the outer strand of a neighboring molecule. See Lockhart at column 22, lines 54-59. Applicants' probes are, instead, intended to complex with the sample labeled DNA. Therefore, one skilled in the art would have no motivation to look to Lockhart et al. to form an array of Applicants' invention.

As evidenced by Guo et al. 1994, page 5459, second column, it was well known in the art at the time of filing that the "surface density of the oligonucleotide probe" is "an important parameter," evidencing the criticality of the claimed density range. This is confirmed by the post-filing reference of Peterson et al., "The effect of surface probe density on DNA hybridization," *Nucleic Acids Research* (2001) Vol. 29, No. 24, 5163-5168.

The area,  $A$ , of a 2-dimensional spot (i.e., a circle) is:  $A = \pi * r^2$

$A = 250\text{--}450 \text{ \AA}^2$  per molecule corresponds to  $r = 8.9\text{--}12.0 \text{ \AA}$  per molecule

Diameter,  $d$ , is:  $d = 2r$ , which can be used to represent the center-to-center distance between two molecules

Thus, Applicants' range of  $250\text{--}450 \text{ \AA}^2$  per molecule would correspond to  $18\text{--}24 \text{ \AA}$ , which is considerably less than the  $100 \text{ \AA}$  spacing found in Lockhart et al.

The density limitation of claim 10 has been incorporated into independent claim 1, and claim 10 has been cancelled herein. Applicants respectfully assert that claims 1 and 11 are not obvious over Bettinotti et al. in view of Sapolsky et al., and further in view of Lockhart et al., and respectfully request that this rejection be withdrawn.

**D. Bettinotti et al. in view of Sapolsky et al. and further in view of Guo et al.**

Claims 10 and 11 are rejected under 35 U.S.C. § 103(a) over Bettinotti et al. (1997) in view of European Patent No. EP0785280 to Sapolsky et al. (1997), and further in view of Guo et al. (1994).

Guo et al. discusses the optimization of the surface density of an array of 15mer oligonucleotides with 15mer oligo dT spacers, representing 5 point mutations from exon 4 of the human tyrosinase gene (see Table 1, page 5459). On page 5460, Guo et al. concludes that an optimum surface density for this system is approximately 500 angstrom<sup>2</sup>/molecule, occurring at about 5mM oligonucleotide concentration (see also Figure 3b, page 5461). Further testing used this optimal concentration of 5mM oligonucleotide.

First, for the reasons stated above, even without the density limitations, claims 1-8 are not obvious over Bettinotti et al. in view of Sapolsky et al., and the elements and suggestions missing from these references are not provided by Guo et al. In contrast to the polymorphisms screened for in the methods of Sapolsky et al., and as noted in Applicants' specification on page 2, lines 14-15, "The human major histocompatibility genes are among the most polymorphic genes known in the human genome." Applicants' arrays for typing HLA loci have to account for this high level of polymorphisms in their probe designs, as described in the specification: "The key feature of the oligonucleotide array assay is the high redundancy of oligonucleotide probes." (page 33, lines 14-15).

The Office Action suggests that "approximately 500 angstrom<sup>2</sup>/molecule" is sufficient to satisfy the density limitations of claims 10 and 11, which recite surface densities of "from about 250 to about 450 angstrom<sup>2</sup>/molecule" and "from about 325 to about 375 angstrom<sup>2</sup>/molecule," respectively. Applicants respectfully disagree.

In light of the above discussion, Guo et al. does not teach or suggest an array having the density limitations contained in independent claims 1 and 25.

## VI. New Claims 51-58

New claims 51-58 are added herein the complete the record and depend from and incorporate the limitations of either independent claim 1 (claims 51-55) or independent claim 25 (claims 56-62). They are, therefore, novel and nonobvious for the reasons set forth above with respect to claims 1 and 25.

In addition, new claims 51 and 55 correspond to original claim 11, but do not contain the term "about" to describe the density range. These density ranges further distinguish the references cited above by giving the claimed ranges more definitive end points.

New claims 52-54 and 56-58 add the limitations that the oligonucleotides are covalently attached to the solid support with a linking group comprising an aminoalkylsilane and a phenylenediisothiocyanate. With the sole exception of the Guo et al. (1994) reference, none of the references cited above teach or suggest these claim limitations. The Guo et al. (1994) reference is distinguished from independent claims 1 and 25, as discussed above.

New claims 52-53 and 55-56 further add the limitations that the array comprises spots of oligonucleotides ranging from 100 to 150 microns in diameter (new claims 52 and 55), and the center of each of said spots is 400-500 microns apart (new claims 53 and 56) (see specification at page 34, lines 21-25). Each of these limitations is neither taught nor suggested by Guo et al. Specifically, Guo et al. discusses an array of oligonucleotides prepared by immersing pre-cleaned microscope slides in 1% 3-aminopropyltrimethoxysilane solution for 2 minutes. However, Applicants' specification teaches of a vapor deposition of the aminoalkyltrialkoxysilane. As discussed on page 27 of the Applicants' specification, the use of a vapor phase deposition of the aminoalkyltrialkoxysilane surprisingly resulted in a particularly uniform surface for probe assembly and presentation, allowing for a more dense array of oligonucleotide probes than the methods discussed in the Guo et al. reference. In contrast to the limitations in new claims 52-54 and 55-58, the spots used by the Guo et al. reference were 3 millimeters wide (see page 5458, bottom of left column).

**VII. Conclusion**

In light of the foregoing, an early and favorable reconsideration and allowance of the pending claims is respectfully requested.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Sherry L. Murphy', written over a horizontal line.

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